ORIGINAL ARTICLE

Global Effect of Modifiable Risk Factors on Cardiovascular Disease and Mortality

The Global Cardiovascular Risk Consortium

ABSTRACT

BACKGROUND

Five modifiable risk factors are associated with cardiovascular disease and death from any cause. Studies using individual-level data to evaluate the regional and sex-specific prevalence of the risk factors and their effect on these outcomes are lacking.

METHODS

We pooled and harmonized individual-level data from 112 cohort studies conducted in 34 countries and 8 geographic regions participating in the Global Cardiovascular Risk Consortium. We examined associations between the risk factors (body-mass index, systolic blood pressure, non–high-density lipoprotein cholesterol, current smoking, and diabetes) and incident cardiovascular disease and death from any cause using Cox regression analyses, stratified according to geographic region, age, and sex. Population-attributable fractions were estimated for the 10-year incidence of cardiovascular disease and 10-year all-cause mortality.

RESULTS

Among 1,518,028 participants (54.1% of whom were women) with a median age of 54.4 years, regional variations in the prevalence of the five modifiable risk factors were noted. Incident cardiovascular disease occurred in 80,596 participants during a median follow-up of 7.3 years (maximum, 47.3), and 177,369 participants died during a median follow-up of 8.7 years (maximum, 47.6). For all five risk factors combined, the aggregate global population-attributable fraction of the 10-year incidence of cardiovascular disease was 57.2% (95% confidence interval [CI], 52.4 to 62.1) among women and 52.6% (95% CI, 49.0 to 56.1) among men, and the corresponding values for 10-year all-cause mortality were 22.2% (95% CI, 16.8 to 27.5) and 19.1% (95% CI, 14.6 to 23.6).

CONCLUSIONS

Harmonized individual-level data from a global cohort showed that 57.2% and 52.6% of cases of incident cardiovascular disease among women and men, respectively, and 22.2% and 19.1% of deaths from any cause among women and men, respectively, may be attributable to five modifiable risk factors. (Funded by the German Center for Cardiovascular Research (DZHK); ClinicalTrials.gov number, NCT05466825.)

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A list of the investigators in the Global Cardiovascular Risk Consortium is provided in the Supplementary Appendix, available at NEJM.org.

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This article was published on August 26, 2023, at NEJM.org.

This is the *New England Journal of Medicine* version of record, which includes all *Journal* editing and enhancements. The Author Accepted Manuscript, which is the author's version after external peer review and before publication in the *Journal*, is available at PubMed Central.

DOI: 10.1056/NEJMoa2206916

Cardiovascular diseases are the most common noncommunicable conditions worldwide and account for approximately one third of all deaths globally.[1] Modifiable risk factors such as body-mass index, systolic blood pressure, low-density lipoprotein cholesterol level, tobacco smoking, and diabetes account for a percentage of the prevalence and incidence of cardiovascular disease; however, the percentage varies according to the populations studied and the methods used.[2,3] These risk factors are used to derive contemporary risk scores[4-6] for the estimation of the 10-year risk of cardiovascular disease, although they are given different weights. These cardiovascular risk factors also have different associations with cardiovascular and noncardiovascular outcomes. Tobacco use is strongly associated with premature death, whereas elevated blood pressure and non–high-density lipoprotein (HDL) cholesterol level are more specifically related to cardiovascular disease.[7]

A tailored reduction in the burden of cardiovascular disease and death from any cause for persons and populations can be achieved with a better understanding of the region- and sex-specific associations of these cardiovascular risk factors with the development of cardiovascular disease. The Global Cardiovascular Risk Consortium analyzed a global harmonized individual-level data set of population-based cohorts to overcome the limitations of summary data and methodologic heterogeneity.

Methods

Study Design and Oversight

The study was designed by the Global Cardiovascular Risk Consortium Management Group, whose members are listed in the Supplementary Appendix, available with the full text of this article at NEJM.org. Data were collected by the Hamburg Data Center. Analyses were performed by the second author and reviewed by the Global Cardiovascular Risk Consortium Statistical Working Group. The first draft of the manuscript was prepared by the first, second, and last authors and was reviewed and edited by all the authors. The authors jointly agreed to submit the manuscript for publication and vouch for the accuracy and completeness of the data and for the fidelity of the study to the protocol.

Study Population

We pooled and harmonized individual-level data from 1,518,028 participants in 112 cohort studies conducted in eight geographic regions (North America, Latin America, Western Europe, Eastern Europe and Russia, North Africa and the Middle East, sub-Saharan Africa, Asia, and Australia) participating in the Global Cardiovascular Risk Consortium. Data were harmonized by applying the variable definitions used by the MORGAM (MONICA [Multinational Monitoring of Trends and Determinants in Cardiovascular Diseases] Risk, Genetics, Archiving, and Monograph) project.[8] Investigators in the studies that were not part of the MORGAM project were sent a list of study-related variables with definitions and were asked to provide these data. A description of each study cohort and information about the local ethics committees and participant informed consent are provided in the Supplementary Appendix. The cohorts that were included in the Global Cardiovascular Risk Consortium were selected on the basis of literature review, existing collaborations among investigators, and the availability of the variables of interest (Table S1). The flow of participants through the study is shown in Figure S1 in the Supplementary Appendix.

Cardiovascular Risk Factors and Outcome Definitions

Five risk factors (body-mass index, systolic blood pressure, non-HDL cholesterol, current smoking, and diabetes) and two outcomes (cardiovascular disease and death from any cause) were assessed in the study because of the heterogeneity of the effects of the risk factors on outcomes and the widespread availability of these data in the population. Further, these risk factors can be modified with interventions. Information on these five modifiable risk factors was collected at baseline according to the protocols of the respective studies included in the Global Cardiovascular Risk Consortium. The standardized definitions that were used to classify cardiovascular disease events are provided in Table S2, and the representativeness of the study population is shown in Table S3.

Statistical Analysis

Missing data were imputed by means of multiple imputation with chained equations (Table S4).[9] Both crude and age- and sex-standardized base-

line characteristics were calculated according to region with the use of direct standardization, with the age and sex distribution of the Global Cardiovascular Risk Consortium data set as the standard. Age-standardized event rates stratified according to region were also estimated and reported per 1000 person-years. Cumulative incidence curves were generated for cardiovascular disease and death from any cause. Associations between risk factors and outcome events were evaluated with the use of a two-stage, multivariate, random-effects meta-analysis of individual participant data.[10] Sex-specific Cox models, with age as the time scale,[11] were computed for each study, and coefficients were pooled across studies according to region as well as globally. Covariates (body-mass index, systolic blood pressure, non-HDL cholesterol level, current smoking, diabetes, and the use of antihypertensive medications) were included simultaneously in the models. Both linear and restricted cubic spline models for continuous covariates and models that allowed for time-varying effects were performed. Models that included receipt of lipid-lowering medications as an additional covariate were also computed with the use of data from the studies in which this information was available (these data were missing for approximately 20% of participants).

For the five modifiable risk factors, region- and sex-specific population-attributable fractions were estimated for the 10-year incidence of cardiovascular disease and 10-year all-cause mortality (see the Supplementary Appendix). Population-attributable fraction is an estimate of the proportion of an outcome that could be prevented if the value of a risk factor were replaced by a hypothetical, ideal value. The approach used by Laaksonen and colleagues,[12] which takes into account the time-to-event nature of the data, was applied to calculate the population-attributable fractions. Weibull models were used in the estimation, and their distributional assumptions were assessed graphically. Reference categories for the risk factors are provided in the Supplementary Appendix.

All the models that were used in the analyses of associations and population-attributable fractions were run with the exclusion of first-year follow-up data (1-year landmark analysis). Two-year landmark analyses that excluded data from the first 2 years of follow-up were performed as sensitivity analyses. The widths of the confidence intervals have not been adjusted for multiple comparisons and should not be used in place of hypothesis testing. All statistical analyses were performed with the use of R software, version 4.1.3.[13]

RESULTS

PARTICIPANT CHARACTERISTICS AND PREVALENCE OF RISK FACTORS

The baseline examination for all study cohorts included in the Global Cardiovascular Risk Consortium took place between 1963 and 2020. In the age- and sex-standardized analysis of data from 1,518,028 participants (54.1% of whom were women) with a median age of 54.4 years, the median body-mass index (the weight in kilograms divided by the square of the height in meters) was 26.4 (interquartile range, 23.7 to 29.7), the median systolic blood pressure 130 mm Hg (interquartile range, 118 to 144), and the median non-HDL cholesterol level 156.9 mg per deciliter (4.06 mmol per liter; interquartile range, 128.8 to 187.9 mg per deciliter [3.33 to 4.86 mmol per liter]); 21.6% were current smokers and 8.3% had diabetes. The age- and sex-standardized prevalence of the five risk factors and the use of antihypertensive and lipid-lowering medications across geographic regions are shown in Table 1 and Table S5. Baseline characteristics without age and sex standardization are shown in Table S6, and the distributions of the risk factors according to sex are shown in Tables S7 and S8. The prevalence of modifiable risk factors across contemporary national health examination surveys, which were used in the population-attributable fraction analyses, is shown in Tables S9, S10, and S11.

CARDIOVASCULAR DISEASE AND DEATH FROM ANY CAUSE

The median duration of follow-up among participants was 7.3 years (interquartile range, 5.9 to 11.8; maximum, 47.3) for incident cardiovascular disease and 8.7 years (interquartile range, 7.0 to 15.9; maximum, 47.6) for death from any cause. The follow-up times for each of the individual cohorts are provided in Table S12. A total of 80,596 cardiovascular disease events (30,033 in women and 50,563 in men) and 177,369 deaths from any cause (78,608 in women and 98,761 in men) were observed during the follow-up period

Table 1. Characteristics of the Cohort Studies and Age- and Sex-Standardized Characteristics of the Participants at Baseline According to Geographic Region.*

Characteristic	Global	North America	Latin America	Western Europe	Eastern Europe and Russia	North Africa and the Middle East	Sub-Saharan Africa	Asia	Australia
Cohort studies									
Cohort studies — no.	112	11	10	58	16	5	2	4	6
Participants — no.	1,518,028	65,182	191,244	907,760	51,133	185,608	10,390	59,802	46,909
Range of survey years†	1963–2020	1971–2011	1990–2013	1970–2015	1983–2014	1963–2020	2011–2017	1988–2015	1983–2007
Participants									
Median age (IQR) — yr‡	54.4 (4.2–63.0)	54.0 (45.0–63.0)	54.0 (45.0–63.0)	54.6 (45.5–63.0)	54.1 (45.5–63.0)	54.0 (45.0–62.6)	54.0 (45.0–63.0)	54.0 (45.0–63.0)	54.6 (45.5–63.0)
Male sex — %‡	45.9	45.9	45.9	45.9	45.9	45.9	45.9	45.9	45.9
Median BMI (IQR)	26.4 (23.7–29.7)	27.2 (24.1–31.0)	28.2 (25.4–31.5)	26.1 (23.6–29.2)	27.2 (24.3–30.6)	27.0 (24.0–30.3)	21.0 (19.0–23.4)	22.8 (20.5–25.2)	26.4 (23.7–29.5)
Median SBP (IQR) — mm Hg	130.0 (118.0–144.0)	122.0 (111.0–136.0)	126.7 (118.0–138.7)	134.0 (122.0–148.0)	132.0 (120.0–148.0)	115.0 (105.0–130.0)	125.0 (113.0–140.0)	123.5 (112.0–136.0)	127.0 (116.5–139.0)
Median DBP (IQR) — mm Hg	80.0 (72.0–87.5)	74.0 (67.0–81.0)	82.7 (76.7–90.0)	81.0 (74.0–89.0)	82.0 (75.0–91.0)	75.0 (67.5–80.0)	75.0 (69.0–83.0)	76.0 (68.0–84.0)	72.5 (64.5–80.5)
Median non-HDL cholesterol (IQR) — mg/dl	156.9 (128.8–187.9)	150.0 (123.0–179.4)	156.2 (131.1–185.2)	162.8 (134.8–193.8)	162.4 (135.0–191.8)	140.1 (115.3–167.8)	116.0 (77.3–154.7)	140.0 (117.6–167.0)	151.2 (124.5–181.0)
Current smoking — %	21.6	22.5	30.8	20.9	29.2	14.2	18.6	23.5	14.3
Diabetes — %	8.3	13.0	15.3	4.8	9.0	18.3	2.0	5.1	4.8
Antihypertensive medications — %	19.4	27.5	19.3	17.9	28.8	24.7	18.5	11.6	13.7
Lipid-lowering medications — %	9.6	8.0	2.3	11.5	8.8	11.6	NA	4.4	4.1
History of CVD — %	5.6	7.2	3.6	5.6	11.2	5.6	0	6.3	7.2

* Percentages are presented for binary variables. Percentages, medians, and interquartile ranges (IQRs) are based on data from the available number of cases per variable. Percentages, medians, and IQRs per geographic region were computed with the use of direct standardization according to age (≤40 years, >40 to ≤45 years, >45 to ≤50 years, >50 to ≤55 years, >55 to ≤60 years, >60 to ≤65 years, >65 to ≤70 years, and >70 years) and sex distribution in the Global Cardiovascular Risk Consortium data set. To convert the values for non–high-density lipoprotein (HDL) cholesterol to millimoles per liter, multiply by 0.02586. BMI denotes body-mass index, CVD cardiovascular disease, DBP diastolic blood pressure, NA data not available, and SBP systolic blood pressure.

† The approximate number of observations according to categorized examination year were 198,517 (13.1%) between 1963 and 1989, 227,002 (15.0%) between 1990 and 1999, 746,074 (49.1%) between 2000 and 2009, and 342,887 (22.8%) between 2010 and 2020.

‡ Similar values for the characteristics of age and sex across the geographic regions are due to the age and sex standardization.

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Table 2. Age-Standardized Outcomes According to Geographic Region and Sex.*

Region	CVD Events among Women			CVD Events among Men			Deaths from Any Cause among Women			Deaths from Any Cause among Men		
	No. of Events	10-yr Incidence (95% CI)	Events per 1000 person-yr (95% CI)	No. of Events	10-yr Incidence (95% CI)	Events per 1000 person-yr (95% CI)	No. of Events	10-yr Incidence (95% CI)	Events per 1000 person-yr (95% CI)	No. of Events	10-yr Incidence (95% CI)	Events per 1000 person-yr (95% CI)
		%	*no.*		%	*no.*		%	*no.*		%	*no.*
Global	30,033	4.0 (4.0–4.1)	5.2 (5.2–5.3)	50,563	7.8 (7.7–7.9)	9.9 (9.8–10.0)	78,608	6.1 (6.0–6.2)	9.0 (9.0–9.1)	98,761	9.3 (9.2–9.4)	13.4 (13.3–13.4)
North America	4,702	7.4 (7.1–7.8)	10.1 (9.8–10.4)	5,321	13.7 (13.1–14.2)	16.6 (16.2–17.1)	8,674	7.6 (7.3–8.0)	16.7 (16.4–17.0)	8,128	11.3 (10.8–11.8)	21.4 (20.9–21.8)
Latin America†	71	—	2.4 (1.9–3.1)	89	—	4.1 (3.3–5.0)	12,488	6.8 (6.6–7.0)	7.5 (7.4–7.7)	9,733	9.7 (9.5–10.0)	10.7 (10.4–10.9)
Western Europe	22,212	3.7 (3.6–3.8)	4.9 (4.8–4.9)	40,942	7.3 (7.2–7.5)	9.6 (9.5–9.7)	42,676	5.6 (5.5–5.7)	8.9 (8.8–9.0)	59,447	8.4 (8.3–8.5)	12.7 (12.6–12.8)
Eastern Europe and Russia	1,078	5.7 (5.0–6.4)	8.7 (7.9–9.5)	1,508	9.9 (8.9–10.9)	13.5 (12.4–14.6)	3,255	10.1 (9.5–10.7)	12.7 (12.2–13.3)	4,827	17.9 (17.1–18.6)	22.1 (21.4–22.8)
North Africa and the Middle East	1,146	6.4 (5.6–7.2)	4.0 (3.7–4.3)	1,805	9.4 (8.5–10.2)	6.8 (6.5–7.2)	1,650	8.1 (7.2–9.0)	6.1 (5.7–6.5)	8,615	11.9 (11.3–12.5)	16.2 (15.8–16.6)
Sub-Saharan Africa‡	3	—	—	1	—	—	431	27.2 (16.0–36.9)	14.1 (12.7–15.6)	456	34.6 (25.1–42.9)	26.7 (24.1–29.6)
Asia	311	2.5 (1.8–3.2)	2.5 (2.2–2.9)	353	4.2 (3.0–5.4)	5.1 (4.5–5.9)	6,399	11.0 (9.9–12.0)	7.6 (7.1–8.1)	4,751	16.7 (15.1–18.4)	12.0 (11.2–13.0)
Australia	510	4.9 (4.3–5.5)	6.0 (5.4–6.6)	544	9.2 (8.3–10.1)	10.3 (9.4–11.4)	3,035	4.7 (4.5–5.0)	5.6 (5.4–5.9)	2,804	7.2 (6.8–7.6)	8.9 (8.5–9.3)

* Computations were performed with the use of data from 1,088,670 participants in the analysis of cardiovascular disease and from 1,419,699 participants in the analysis of all-cause mortality. The 10-year incidence of events was estimated with the use of the Kaplan–Meier estimator. Events per 1000 person-years were estimated with the use of data obtained during the complete follow-up, and a Poisson regression with log-transformed follow-up time was used as an offset. Direct standardization according to the age distribution in the Global Cardiovascular Risk Consortium data set (≤40 years, >40 to ≤45 years, >45 to ≤50 years, >50 to ≤55 years, >55 to ≤60 years, >60 to ≤65 years, >65 to ≤70 years, and >70 years) was used in the computation of the 10-year incidence of events and events per 1000 person-years per geographic region. The widths of the 95% confidence intervals have not been adjusted for multiplicity and should not be used in place of hypothesis testing.

† Because the CVD follow-up in Latin America is shorter than 10 years, it is not possible to obtain an estimate of the 10-year incidence of the event with the Kaplan–Meier estimator.

‡ Because of the low number of CVD events recorded, the 10-year incidence of events and events per 1000 person-years were not estimated.

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(Table 2). The age-standardized 10-year incidence of cardiovascular disease was 7.4% for women and 13.7% for men in North America, 6.4% for women and 9.4% for men in North Africa and the Middle East, 5.7% for women and 9.9% for men in Eastern Europe and Russia, 3.7% for women and 7.3% for men in Western Europe, and 2.5% for women and 4.2% for men in Asia. The global 10-year incidence of cardiovascular disease was 4.0% among women and 7.8% among men (Table 2). Cardiovascular disease appeared to develop in women at older ages than men (Fig. S2). The age-standardized 10-year all-cause mortality was 27.2% for women and 34.6% for men in sub-Saharan Africa, 10.1% for women and 17.9% for men in Eastern Europe and Russia, 11.0% for women and 16.7% for men in Asia, and 4.7% for women and 7.2% for men in Australia (Table 2).

EFFECTS OF MODIFIABLE RISK FACTORS

The risk factor–associated hazard ratios for cardiovascular disease and death from any cause according to geographic region and sex, as calculated with the exclusion of data from the first year of follow-up (1-year landmark analysis), are shown in Table S13 and Figures S3 through S7. Subdistribution hazard ratios for cardiovascular disease were calculated with death from noncardiovascular causes as the competing event, and the results were similar to those in the 1-year landmark analysis (Table S14). The associations between the risk factors and cardiovascular disease and death from any cause in the models that used continuous risk factors and allowed for nonlinear effects are shown in Figure 1 and Figure S4. In a 2-year landmark analysis that excluded data from the first 2 years of follow-up, the observed associations appeared to be similar to those in the 1-year landmark analysis (Fig. S5), as were the results of other sensitivity analyses (2-year landmark Cox regression models with a linear exposure–effect assumption, models restricted to cohorts starting in the year 2000 or later, models restricted to participants with data on the use of lipid-lowering medications, and

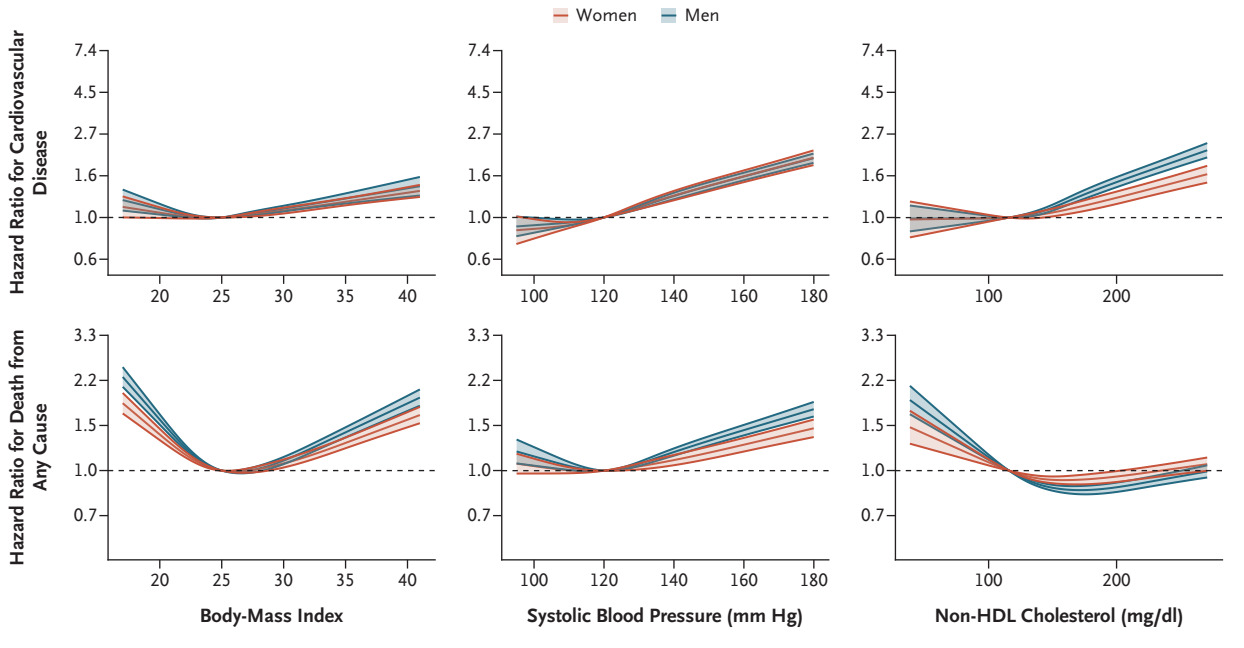

Figure 1. Associations of Continuous Risk Factors with Cardiovascular Disease and Death from Any Cause.

Shown are the results of a global 1-year landmark analysis that allowed for nonlinear effects. Participants with cardiovascular disease at baseline were excluded. Age was used as the time scale. All five risk factors, together with the use of antihypertensive medications, were included as covariates in the models. The widths of the 95% confidence intervals (shaded areas) have not been adjusted for multiplicity and should not be used in place of hypothesis testing. To convert the values for non–high-density lipoprotein (HDL) cholesterol to millimoles per liter, multiply by 0.02586.

models with an alternative definition of cardiovascular disease [a composite of fatal or nonfatal myocardial infarction, ischemic or hemorrhagic stroke, or cardiovascular death]) (Tables S15 through S18 and Fig. S6). Unadjusted risk factor–associated hazard ratios for cardiovascular disease and death from any cause are provided in Table S19. For both cardiovascular disease and death from any cause, the association with body-mass index appeared to be consistent across all ages, whereas the strength of the associations with systolic blood pressure, current smoking (after a steady increase up to the second half of life for death from any cause), and diabetes decreased with age (Fig. 2 and Fig. S7). The strength of the association between non-HDL cholesterol level and cardiovascular disease seemed to decline with age but appeared to be stable for death from any cause.

PREVENTABLE CARDIOVASCULAR DISEASE AND DEATH FROM ANY CAUSE

The distributional assumptions of the models used in the estimations of the population-attributable fractions were examined graphically (Fig. S8). The five modifiable risk factors accounted for an aggregate global population-attributable fraction of the 10-year incidence of cardiovascular disease of 57.2% (95% confidence interval [CI], 52.4 to 62.1) among women and 52.6% (95% CI, 49.0 to 56.1) among men. In comparison, the five risk factors accounted for an aggregate global population-attributable fraction of 10-year all-cause mortality of 22.2% (95% CI, 16.8 to 27.5) among women and 19.1% (95% CI, 14.6 to 23.6) among men (Fig. 3).

For all modifiable risk factors combined, the aggregate population-attributable fraction of the 10-year incidence of cardiovascular disease was

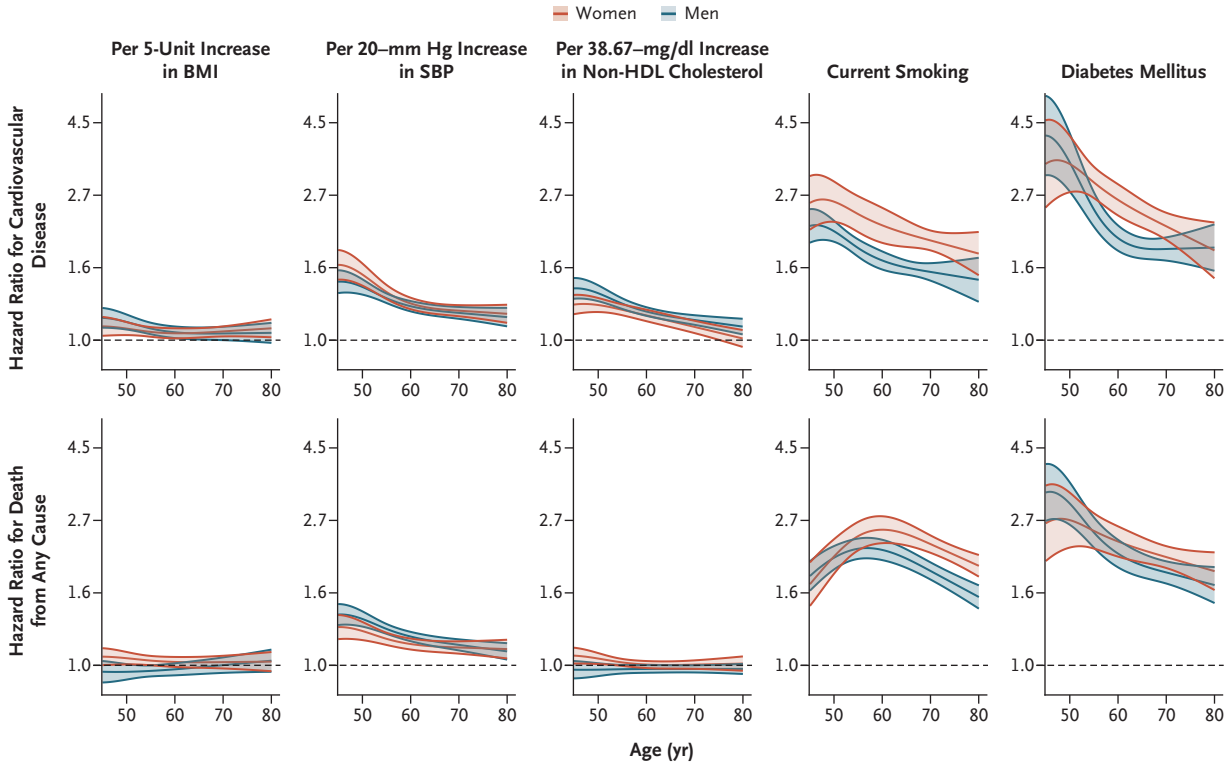

Figure 2. Associations of Risk Factors with Cardiovascular Disease and Death from Any Cause.

Shown are the results of a global 1-year landmark analysis that allowed for effects to change with age. Participants with cardiovascular disease at baseline were excluded. Age was used as the time scale. All five risk factors, together with the use of antihypertensive medications, were included as covariates in the models. The widths of the 95% confidence intervals (shaded areas) have not been adjusted for multiplicity and should not be used in place of hypothesis testing. BMI denotes body-mass index, and SBP systolic blood pressure.

64.2% (95% CI, 59.8 to 68.6) among women and 60.5% (95% CI, 57.2 to 63.9) among men in North Africa and the Middle East and 55.5% (95% CI, 50.7 to 60.3) and 50.3% (95% CI, 46.8 to 53.8), respectively, among those in North America. The aggregate population-attributable fraction of 10-year all-cause mortality was 34.3% (95% CI, 29.7 to 38.9) among women and 43.2% (95% CI, 39.8 to 46.6) among men in Asia; 13.7% (95% CI, 7.1 to 20.3) and 2.9% (95% CI, −3.7 to 9.5), respectively, among those in Australia; and 15.7% (95% CI, 9.3 to 22.0) and 2.1% (95% CI, −4.3 to 8.6), respectively, among those in Western Europe (Fig. 3).

The population-attributable fractions calculated for the individual five modifiable risk factors are shown in Figure S9. The population-attributable fraction of the 10-year incidence of cardiovascular disease associated with systolic blood pressure was 29.3% (95% CI, 25.4 to 33.2) among women and 21.6% (95% CI, 18.7 to 24.5) among

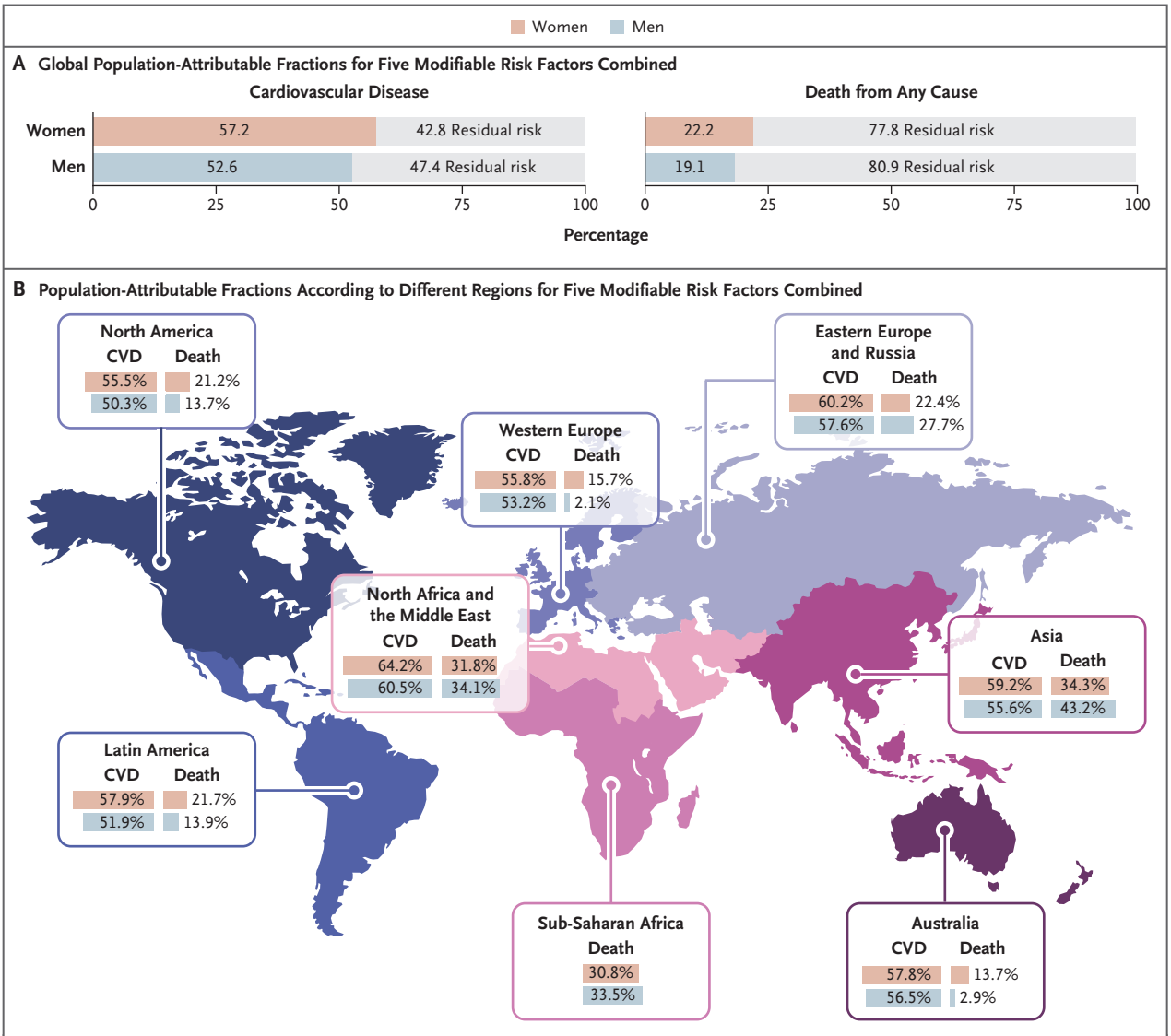

Figure 3. Population-Attributable Fractions of the 10-Year Incidence of Cardiovascular Disease (CVD) and 10-Year All-Cause Mortality.
Population-attributable fractions were estimated with the use of Weibull models. For the five modifiable risk factors combined, the aggregate global population-attributable fractions are shown in Panel A and the aggregate population-attributable fractions according to geographic region are shown in Panel B. Population-attributable fractions for the individual risk factors according to geographic region are provided in Figure S9 in the Supplementary Appendix.

men; the corresponding values were 15.4% (95% CI, 10.9 to 19.8) and 16.6% (95% CI, 12.6 to 20.6) for cardiovascular disease associated with non-HDL cholesterol level and 15.2% (95% CI, 13.3 to 17.1) and 10.2% (95% CI, 9.2 to 11.2) for cardiovascular disease associated with diabetes. The population-attributable fraction of the 10-year incidence of cardiovascular disease among women was 6.7% (95% CI, 5.8 to 7.6) for current smoking and 7.6% (95% CI, 5.1 to 10.1) for body-mass index; the corresponding values among men were 10.7% (95% CI, 9.6 to 11.7) and 7.6% (95% CI, 5.6 to 9.7). Among women, the population-attributable fraction of 10-year all-cause mortality associated with diabetes was 12.2% (95% CI, 11.1 to 13.3), whereas among men, the population-attributable fraction of 10-year all-cause mortality associated with current smoking was 14.4% (95% CI 13.3 to 15.4). The population-attributable fractions of the 10-year incidence of cardiovascular disease and 10-year all-cause mortality, according to modifiable risk factor level or status, are shown in Tables S20 and S21.

DISCUSSION

The Global Cardiovascular Risk Consortium harmonized individual-level data from 1,518,028 participants who participated in 112 cohort studies conducted in 34 countries in North America, Latin America, Western Europe, Eastern Europe and Russia, North Africa and the Middle East, sub-Saharan Africa, Asia, and Australia to assess the effect of five modifiable risk factors on the incidence of cardiovascular disease and all-cause mortality. The study showed that the prevalence of the five modifiable risk factors and the incidence of cardiovascular disease and all-cause mortality varied across geographic regions worldwide, and women had consistently lower event rates than men. The association between individual modifiable risk factors and both incident cardiovascular disease and death from any cause also varied across regions. The five modifiable risk factors accounted for an aggregate population-attributable fraction of the 10-year incidence of cardiovascular disease of 57.2% among women and 52.6% among men, and the corresponding values for 10-year all-cause mortality were 22.2% and 19.1%. Population-attributable fractions of the incidence of cardiovascular disease and all-cause mortality varied according to geographic region. Elevated systolic blood pressure appeared to be the largest contributor to the population-attributable fraction of incident cardiovascular disease events in all regions.

The Global Cardiovascular Risk Consortium and other studies[14-16] confirmed apparent differences in cardiovascular risk factor profile and event rates between women and men, irrespective of geographic region. Differences in risk factor level have been shown to translate into lifetime risk of cardiovascular disease[17] but not necessarily to affect other fatal outcomes. Cardiovascular risk factors are known to increase cardiovascular disease risk differently across various geographic regions.[2,18] Among them, high blood pressure is associated with up to 13.5% of all deaths annually worldwide and is considered to be the leading risk factor for cardiovascular disease.[19] Strict blood-pressure control to a systolic blood pressure of less than 120 mm Hg has been associated with lower rates of cardiovascular events and all-cause mortality.[20] Our data corroborate this observation; of the five risk factors studied, systolic blood pressure may offer the greatest potential for the prevention of cardiovascular disease. Although there is a strong continuous association between non-HDL cholesterol level and incident cardiovascular disease,[21] we and others[3,22,23] observed an inverted J-shaped association of non-HDL cholesterol level with all-cause mortality. Although very low levels of non-HDL cholesterol are related to a reduction in cardiovascular disease events,[24,25] some observations point toward higher all-cause mortality among participants with very low levels, at least in longer-term follow-up.[26] In contrast to what was previously reported,[3] body-mass index and current smoking (at least in some parts of the world) were associated with comparatively modest population-attributable fractions of cardiovascular disease events in the populations participating in the Global Cardiovascular Risk Consortium. These associations may be related to underlying differences in population characteristics, risk-factor definition and prevalence, or methods used to estimate population-attributable fractions.

Case–control studies such as INTERHEART may have overestimated the population-attributable fraction of the incidence of cardiovascular disease subtypes by attributing 90% of the risk of myocardial infarction to nine targetable risk factors.[2] Data from 155,722 participants who were

evaluated prospectively in the Prospective Urban Rural Epidemiology (PURE) study suggested that 71% of cardiovascular disease cases are attributable to 14 potentially modifiable metabolic and behavioral risk factors, a result that is consistent with our findings.[3] Our study focused on five modifiable risk factors for which strict control could potentially prevent 57.2% of all cases of cardiovascular disease in women and 52.6% of all cases in men globally. The varying effect of individual risk factors across different regions could enable ranking and prioritization of risk-factor control for public health action within those regions. However, there is substantial scope for a more complete characterization of the risk of cardiovascular disease. Environmental and exposure-related factors such as physical activity,[2] alcohol consumption,[27] air pollution,[28] climate and noise,[29] educational level,[3] or psychosocial risk factors, including depression,[30] have an effect on the risk of cardiovascular disease. Biomarkers[31,32] and genetic variants most likely would add to the prediction of cardiovascular disease risk.

The analysis by the Global Cardiovascular Risk Consortium differs from other global initiatives that combine different data sources such as registries, population surveys, and health system administrative data to produce meta-analytic summaries.[33,34] The Global Cardiovascular Risk Consortium maintains a large and comprehensive database of harmonized, observational, individual-level, prospectively collected data. This database allows for multiple prespecified statistical analyses on large-scale individual-level data. This study relates major modifiable cardiovascular risk factors to the incidence of cardiovascular disease and all-cause mortality. The inclusion of cohorts with a large spectrum of follow-up times enabled robust sex-specific analyses and the evaluation of differences across geographic regions.

Our study has several limitations. The Global Cardiovascular Risk Consortium database includes cohorts with varying representativeness, data quality and quantity, dates of baseline assessments, follow-up times, end-point definitions, and use of clinical interventions. Variation in the adjudication of causes of death or surrogates of nonfatal myocardial infarction is plausible across regions, but an analysis that included the use of a secondary definition of cardiovascular disease that excluded unclassifiable death, unstable angina, and coronary revascularization did not change the results. Structured harmonization was used to reduce variation, and sensitivity analyses provided results similar to those for the overall study population. Standardized event rates should be interpreted as descriptive measures rather than actual incidences in a population. To overcome bias resulting from deaths from noncardiovascular diseases that were present at the time of the baseline examination, analyses were performed with the exclusion of first-year follow-up data. Information about modifiable risk factors was available from the baseline examination, and the effect of changes in exposure over time are not known; the analyses were not corrected for regression dilution bias. Residual confounding cannot be completely excluded. The effects of overweight and obesity may be mediated by hyperlipidemia, hypertension, and diabetes.[35] Models that included body-mass index, systolic blood pressure, and diabetes attribute the share of the effect of body-mass index to systolic blood pressure and diabetes, even if overweight or obesity is the real underlying cause. The definition of current smoking may not capture the entire spectrum and dose of tobacco exposure, and smoking cessation during follow-up might have led to an underestimation of tobacco smoking as a risk factor. It was also assumed that risk factor effects and prevalence within a region are homogeneous; however, intraregional differences may exist. Information about ethnic group is not provided, because definitions differed among the cohorts or collection of the variable was incomplete or not available to a comparable standard. The categorization of geographic regions by the World Health Organization and United Nations was adapted to accommodate cohort size and representativeness of a geographic region, so a different categorization of regions may produce different results.

In our study, harmonized individual-level data from the Global Cardiovascular Risk Consortium showed that 57.2% and 52.6% of cases of incident cardiovascular disease among women and men, respectively, and 22.2% and 19.1% of deaths from any cause among women and men, respectively, may be attributable to five modifiable risk factors. The prevalence and effect of these risk factors on the incidence of cardiovascular disease and all-cause mortality vary according to sex and geographic region.

Supported by the German Center for Cardiovascular Research (DZHK).

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

APPENDIX

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